COMPOSITIONS AND METHODS FOR TREATING EPIGENETIC DISEASE

CROSS REFERENCE TO RELATED APPLICATIONS

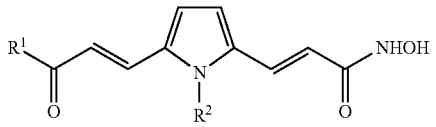
[0001] This application claims the benefit of, and priority to, U.S. Provisional Patent Application No. 62/702,183, filed Jul. 23, 2018, the disclosure of which is incorporated herein by reference in its entirety.

BACKGROUND

[0002] Epigenetic alterations have been involved in the pathogenesis of cancer and auto-immune diseases, including Crohn's Disease, Ulcerative Colitis, Lupus and Rheumatoid Arthritis. Histone deacetylases (HDACs) are enzymes that catalyze the removal of acetyl functional groups from the lysine residues of both histone and non-histone proteins. HDAC enzymes are divided into four different classes: Class I (HDAC 1,2,3,8), Class II (HDAC4,5,6,7,9,10), Class III (SIRT1-7) and Class IV (HDAC11). HDACs 4, 5, 7, & 9 consist the Class IIA. There is an unmet need to develop HDAC inhibitors that are selective for certain HDAC isoforms.

SUMMARY OF THE INVENTION

[0003] In certain aspects, the present disclosure provides a compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R^1 is aryl or heteroaryl; and
R^2 is alkyl.

[0004] In certain aspects, the present disclosure provides methods of treating a disease selected from a cancer or an autoimmune disease in a subject, comprising administering to the subject a compound or composition as disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0005] FIGS. **1**A-**1**D show treatment with MJK-006 resulted in significant differences in colon length, clinical and histological scoring during TNBS colitis as compared to vehicle-treated mice.

[0006] FIGS. **2**A-**2**D show MJK-008 had significant effect in preserving colon length and decreasing the clinical and histological score in comparison to untreated mice. Histological sections show that TNBS induces crypt damage, which was significantly restored after MJK-008 treatment.

[0007] FIGS. **3**A-**3**C show mice treated with MJK-001, MJK-002 and MJK-003 showed statistical significance in the reduction of the clinical score and increase of colon length.

[0008] FIGS. **4**A-**4**D show MJK-004, MJK-005, MJK-009 and MJK-011 administration yielded reduction in clinical scoring but did not alter colon length.

[0009] FIGS. **5**A-**5**D show mice treated with MJK-007, MJK-010, MJK-012 or MJK-013 showed no significant differences from vehicle-treated mice in colon length or clinical scoring.

[0010] FIGS. **6**A-**6**C shows that MJK-008 was highly efficient in reducing the clinical score, preserving colon length and decreasing the histology score.

[0011] FIG. **7** shows that MJK-001 partially blocks both HDAC4 and HDAC9 isoforms, while MJK-006 and MJK-008 have high specificity for the HDAC9 isoform.

[0012] FIG. **8** shows that HDAC9 overexpression results in substantial increase in IL1B and TNFA mRNA levels.

[0013] FIG. **9** shows that MJK-004 reduced significantly the ability of RT-112 bladder cancer cells to form colonies in soft agar.

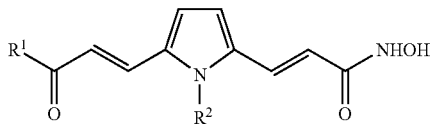
[0014] FIG. **10** shows that MJK-004 has high specificity for HDAC4 and very low activity against HDAC9.

[0015] FIG. **11** shows MJK-004 suppressed bladder cancer growth in both cell lines as a monotherapy. MJK-004 combination with gemcitabine increased gemcitabine's efficacy in RT-112 and UMUC9 bladder cancer cells.

DETAILED DESCRIPTION OF THE INVENTION

[0016] The present disclosure provides small molecule HDAC inhibitors, aiming to target specific isoforms of the HDAC Class IIA members.

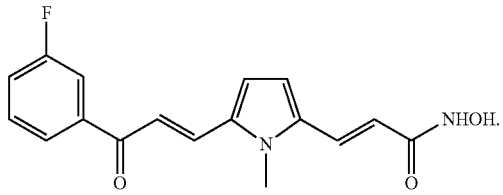
[0017] In certain aspects, the present disclosure provides a compound of formula I, or a pharmaceutically acceptable salt thereof:



(I)

wherein:
R^1 is aryl or heteroaryl; and
R^2 is alkyl.

[0018] In certain embodiments, the compound is not



[0019] In certain embodiments, R^1 is 6-membered aryl or 5- to 6-membered heteroaryl.

[0020] In certain such embodiments, R^1 is phenyl optionally substituted, e.g., at the 2-position, with alkoxy, such as methoxy, or halo, such as chloro.

[0021] In other such embodiments, R^1 is pyrrolyl and is optionally substituted at the N-position with alkyl, such as methyl.

[0022] In yet other such embodiments, R^1 is pyridinyl, pyrazinyl, thiophenyl, or furanyl. In some such embodi-